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PATENT SPECIFICATION

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(72) Inventors ANDRE QUEUILLE, FRANCOISE BRENOT and GENEVIEVE AZADIAN

(54) IMPROVEMENTS IN OR RELATING TO PROCESSES FOR THE PREPARATION OF MICROBEADS AND USE IN THE MICROBEADS THUS PRODUCED IN THE PREPARATION OF INJECTABLE MEDICAMENTS

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7eme, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns improvements in or relating to processes for the preparation of microbeads, and use of the microbeads thus produced in the preparation of injectable medicaments.

It is well recognized that the absorption of pharmaceutically-active substances by organisms is extremely variable, as regards its duration and significance, dependent on the method of administration. In the most favourable cases, absorption can lead to a rapid onset of activity which then can last for several hours. In order to prolong the period of such activity, various expedients have been adopted—thus for instance it is possible to modify the size of the particles of the active ingredient, or to administer it in the form of suspensions or emulsions, or even to provide it with a coating of such a nature that it is liberated very slowly within the organism.

A process for preparing medicaments in the form of beads has been already described in French Patent No. 1,468,716, in which the therapeutically-inactive material used in the preparation of the beads is susceptible to the juices of the digestive tract, and is broken down by them to a greater or a lesser extent, so that it becomes possible to secure a variable absorption by the digestive tract of the active ingredient or ingredients for which the bead is the vehicle. Unfortunately, however, the beads described in French Patent No. 1,468,716, because of their size, seem to be useful only for oral administration.

We have now found that using essentially the same materials as those featured in the aforesaid French Patent No. 1,468,716, but using them in a quite different way, it is possible to prepare microbeads, rather than beads, which retain the active ingredient in a similar manner but which, because of their small size, can be put into suspension in a liquid vehicle, and thus can be administered via the parenteral route. The presentation of the medicaments in this manner has been found to prolong their duration of activity, usually to such an extent that the medicament thus administered displays its activity for very much longer than that achieved on parenteral administration of the corresponding active ingredient alone.

According to the present invention there is therefore provided a process for preparing microbeads which comprise at least one water-insoluble or sparingly water-soluble pharmaceutically-active ingredient enclosed within a mantle composed of at least one methacrylic polymer (as hereinafter defined), the mean diameter of the said microbeads being within the range of from 1 micron to 90 microns, in which an organic phase, comprising the methacrylic monomer or mixture of methacrylic monomers, a cross-linking agent for the monomer(s) and the water-insoluble or sparingly water-soluble pharmaceutically-active ingredient(s), is emulsified in an aqueous phase containing one or more salt(s) under agitation with a rotary stirrer running at a speed of at least 1,000 revolutions per minute, a polymerisation catalyst is then added to the emulsion thus formed, the polymerization is allowed to proceed, and the microbeads thus formed are recovered.

While the microbeads prepared according to this invention may have a mean diameter anywhere within the range just specified, it is especially preferred to employ microbeads whose mean diameter is within the range of from 20 to 50 microns.

The term "methacrylic polymer" as used

herein with reference to the microbeads of the present invention means either a homopolymer of methacrylic acid or of an alkyl methacrylate, or a copolymer of methacrylic acid with an alkyl methacrylate or with or between several alkyl methacrylates. We currently prefer the copolymers of methacrylic acid, methyl methacrylate and butyl methacrylate.

This invention is primarily concerned with the mode of presentation of the pharmaceutically-active ingredients, rather than with the precise nature of those pharmaceutically-active ingredients themselves—which of course are chosen from the viewpoint of therapy. However, it may be said that the pharmaceutically-active ingredients which are of greatest interest when presented in the form of the microbeads of the present invention are most frequently those medicaments which must be administered in small doses over a long period; and thus in general the microbeads of this invention are especiallly useful where the active ingredient(s) include one or more of the following. namely hormones and contraceptive agents, cortico-steroids, antibiotics, anti-inflammatory agents, psychotropic agents, anti-parasitic agents and cytostatic or cytolitic agents.

Preferably the process of the present invention will be performed using an aqueous phase containing one or more salt(s) which also contains an emulsifying agent and/or an anti-coalescing agent. It is also preferred to use an organic phase in the process of the invention which contains not only the methacrylic monomer or mixture of methacrylic monomers, the cross-linking agent for the monomer(s) and at least one pharmaceutically-active ingredient, but also an emulsifying agent, a plasticizing agent and a hardening agent. After the emulsion has been formed by stirring at 1,000 r.p.m. or more, a catalyst is then added to the continuous phase of the emulsion to induce the polymerization which, on completion, yields the microbeads as herein disclosed.

The salt included in the aqueous phase can advantageously be an alkali metal, alkaline earth metal or ammonium sulphate, conveniently for instance sodium or ammonium sulphate.

The emulsifying agent used in the aqueous phase can advantageously be a sorbitan polyoxyethylene monooleic ester, such as the one known as "polysorbate 80".

The anti-coalescing agent used in the aqueous phase can advantageously be a carboxyvinylic polymer, such as the product sold commercially under the Mark "Carbopol 961" (the word "Carbopol" is a Registered Trade Mark).

The methacrylic monomer or mixture of methacrylic monomers used in the organic phase of the process of the invention will be chosen in accordance with the desired end-product. Usually however the monomer(s) used will be one or a mixture of more than one of the following, namely methacrylic acid and alkyl methacrylates, particularly methyl methacrylate or butyl methacrylate.

The cross-linking agent for the monomer used in the organic phase of the process of the invention is preferably divinylbenzene.

The emulsifying agent used in the organic phase of the process of the invention can conveniently be a mixture of saturated high molecular weight fatty acid mono- and diglycerides, such as for instance the product sold under the Mark "Cutina M.D.".

The plasticizing agent used in the organic phase of the process of the invention can advantageously be an alkyl sebacate, and especially diethyl or dioctyl sebacate.

The hardening agent used in the organic phase of the process of the invention is preferably polyvinyl acetate; and the catalyst used therein is preferably 2,2'-azo *bis-iso*-butyronitrile.

The emulsification of the organic phase in the aqueous phase is desirably effected at a temperature within the range of from 60°C to 90°C.

The invention of course also extends to microbeads whenever prepared in or by the process herein described.

Moreover, in another aspect of the invention, there are also provided pharmaceutical compositions which comprise the microbeads prepared by the process herein described suspended or otherwise dispersed in a suitable aqueous or oily pharmaceutical vehicle to form a sterile injectable dispersion.

The term "suitable pharmaceutical vehicle" is used herein to exclude any possibility that the nature of the vehicle, considered of course in relation to the parenteral route by which the composition is intended to be administered, could be harmful rather than beneficial. The choice of an appropriate vehicle is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

It is the particular advantage of the microbeads of this invention that they can, by reason of their small diameter, be administered transcutaneously, that is to say by an intramuscular or subcutaneous route, in the form of suspension in an aqueous or oily vehicle to form a sterile injectable liquid dispersion. Such injectable liquid dispersions may be dispensed in single-dose ampoules or mult-dose phials. It may here be noted that the microbeads of the present invention, when injected into man by the intramuscular route, are excellently tolerated and give the useful results hereinafter illustrated.

In order that the invention may be well understood it will now be further described, though only for purposes of illustration, in the following Examples:—

Example 1.

Preparation of Microbeads of Testosterone Acetate

An aqueous phase is prepared by mixing together the following ingredients:—

Carboxyvinylic polymer (Carbopol 961)	0.75 g
Sodium carboxymethylcellulose	0.18 g
Sodium sulphate (anhydrous)	25.00 g
Polysorbate 80	0.30 g
Distilled water	165.00 g

The aqueous phase thus obtained is placed in a water bath at 70°C, and agitated by stirring at 11,000 revolutions per minute.

While maintaining the agitation and the temperature at 70°C, to the aqueous phase there is then added an organic phase prepared by mixing together the following ingredients:—

Methyl methacrylate	10.00 g
Butyl methacrylate	4.00 g
Methacrylic acid	7.00 g
Divinylbenzene (50%) in ethyl vinylbenzene	13.00 g
Crotonic acid	0.52 g
Polyvinyl acetate	2.00 g
Diethyl sebacate	1.00 g
Cutina M.D.	1.00 g
Anti-foaming agent	0.10 g
Testosterone acetate	9.50 g

When emulsification of the two phases is complete, the emulsified mixture is rapidly poured into a flask fitted with a reflux condenser and a stirrer, and a current of inert gas is passed through the flask while the temperature is maintained at about 70—80°C and the stirrer is run at 1,000 revolutions per minute.

After ten minutes' agitation, 300 mg of ammonium persulphate is introduced into the reaction mixture, followed, after half an hour, by 100 mg of 2,2' - azo *bis-iso*butyronitrile.

The agitation is then continued for several hours, after which the contents of the flask are poured into a large quantity of cold water. The microbeads thus obtained are separated, graded on a sieve, and oven dried. After drying, the mean diameter of the microbeads thus obtained is within the range of from 1 to 5 microns.

Example 2.

Preparation of Microbeads of Testosterone Acetate

An aqueous phase is prepared in a manner identical to that of Example 1. This aqueous phase is placed in a water bath at 70°C, and agitated by stirring at 11,000 revolutions per minute.

While maintaining the agitation and the temperature at 70°C, to the aqueous phase there is then added an organic phase prepared by mixing together the following ingredients:—

Methyl methacrylate	10.00 g
Butyl methacrylate	4.00 g
Methacrylic acid	7.00 g
Divinylbenzene (50%) in ethyl vinylbenzene	13.00 g
Crotonic acid	0.52 g
Polyvinyl acetate	2.00 g
Diethyl sebacate	1.00 g
Cutina M.D.	1.00 g
Anti-foaming agent	0.10 g
Anhydrous petroleum-ether (D.P. 40—70°C)	200 ml

When emulsification of the two phases is complete, 10 g of micronised testosterone acetate is added in very small amounts and under agitation at 11,000 revolutions per minute.

The mixture is poured into a flask fitted with a reflux condenser and a stirrer. The temperature is maintained at 75—80°C, and the stirrer is run at 1,000 revolutions per minute.

After driving off the air by refluxing the petroleum ether for ten minutes, 300 mg of ammonium persulphate is introduced into the reaction media, followed after a half hour by 100 mg of 2,2' - azo - *bis* - *iso*butyronitrile.

Agitation is then maintained for another five hours, after which the petroleum ether is evaporated off under reduced pressure, water being added in proportion to the petroleum ether distilled off. The mixture is then cooled to ambient temperature, diluted in about a litre of cold water, and the microbeads are filtered off using a sieve.

After oven drying, the mean diameter of the microbeads thus obtained lies in the range of from 1 to 2 microns.

Example 3.

Preparation of Microbeads of Chlorpromazine

An aqueous phase is prepared by mixing together the following ingredients:—

Carboxyvinylic polymer (Carbopol 961)	0.150 g
Polysorbate 80	0.100 g
Sodium sulphate (anhydrous)	7.500 g
Distilled water	37.500 g

The aqueous phase thus obtained is placed in a water bath at 70°C.

Separately, an organic phase is prepared by mixing together the following ingredients:—

α-Methacrylic acid	5.000 g
Polyvinyl acetate (Rhodopas BB)	2.000 g
Divinylbenzene(50%) in ethyl vinylbenzene	3.000 g
Cutina M.D.	0.100 g

The mixture is warmed to dissolve the polyvinyl acetate, and then 2.5 g of chlorpromazine are added thereto.

The organic phase thus prepared is then poured into the aqueous phase, and the mixture is stirred at 1,000 revolutions per minute while the temperature of the mixture is adjusted to and maintained at about 70°C.

When emulsification of the two phases is completed, 100 mg of azo-*iso*-butyronitrile is added, and after three to four hours the polymerisation has gone to completion. The microbeads thus formed are then poured into about one litre of cold water, washed, and separated by decantation. After oven drying and sieving, the microbeads recovered have a mean diameter of less than 90 microns.

Example 4.

Preparation of Microbeads of Testosterone Acetate

An aqueous phase is prepared by mixing together the following ingredients:—

Carboxyvinylic polymer (Carbopol 961)	0.60 g
Sodium sulphate (anhydrous)	30.00 g
Polysorbate 80	0.30 g
Distilled water	150.00 g

Separately, an organic phase is prepared by mixing together the following ingredients:—

α-Methacrylic acid	20.00 g
Polyvinyl acetate	7.36 g
Crotonic acid	0.64 g
Divinylbenzene (50%)	12.00 g
Testosterone acetate	10.00 g

The organic phase is emulsified in the aqueous phase at a temperature of about 70°C, by agitation at about 1,200 revolutions per minute, and 300 mg of 2,2' - azo - *bis* - *iso*-butyronitrile is then added.

Agitation is continued for several hours, then the contents of the flask are poured into a large quantity of cold water.

The microbeads thus obtained are sorted by sieving, and the mean diameter of the bulk of the microbeads is found to be between 50 and 60 microns.

Example 5.

Preparation of Microbeads of 13β-Ethyl-17α - ethynyl - 17β - hydroxy - gona-4,9,11 - trien - 3 - one

An aqueous phase is prepared by mixing together the following ingredients:—

Carboxyvinylic polymer (Carbopol 961)	0.300 g
Sodium sulphate (anhydrous)	15.0 g
Hydrophilic emulsifying agent (Polysorbate 80)	0.8 g
Distilled water to make	75.0 g

The aqueous phase obtained is placed in a water bath at 80°C, and agitated by stirring at 11,000 revolutions per minute.

While maintaining the agitation, and the temperature at about 80°C, to the aqueous phase there is then added an organic phase prepared by mixing together the following ingredients:

α-Methacrylic acid	10 g
Polyvinyl acetate (Rhodopas BB)	3.6 g
Crotonic acid	0.32 g
Divinylbenzene (50%) in ethyl vinylbenzene	6.0 g
Plasticizing agent	0.5 g
13β - Ethyl - 17α - ethynyl - 17β-hydroxy - gona - 4,9,11 - trien-3 - one	1.116 g

Agitation is continued, by stirring at a rate of about 1,200 revolutions per minute, until the organic phase has been emulsified in the aqueous phase, and then 0.2 g of 2,2' - azo-*bis* - *iso*butyronitrile is added in two portions at an interval of thirty minutes.

Agitation is continued for several hours further, and then the whole mixture is poured into a large quantity of cold water. The microbeads thus formed are washed several times with water, dried, and sorted by sieving.

The mean diameter of the dried microbeads thus obtained lies in the range of from 60 to 75 microns.

Example 6.

Formulation of Injectable Preparation

The microbeads prepared as described in Example 1 (containing 20% w/w of testosterone acetate) were mixed with an aqueous excipient (containing a preservative) to form an injectable preparation, in the following proportions:—

Microbeads of testosterone acetate	100 mg
Aqueous excipient, to make	2 ml

Example 7.

Preparation of Injectable Suspension

Microbeads containing 20% w/w of chlorpromazine were mixed with an aqueous excipient (containing a preservative) to form an injectable suspension, in the following proportions:—

Microbeads of chlorpromazine	12.50 g
Aqueous excipient, to make	100 ml

The suspension thus formed is loaded into 5 ml ampoules and sterilized.

Example 8.

Preparation of Injectable Suspension

The microbeads prepared as described in Example 4 (containing 20% w/w of testosterone acetate, and 80% w/w of polymer coating) were mixed with an aqueous excipient to

form an injectable suspension in the following proportions:—

Microbeads of testosterone acetate	6.25 g
Aqueous excipient, to make	250 ml

The suspension thus formed is loaded into 5 ml ampoules, and sterilized.

Example 9.
Tests for Duration of Activity

A study of the duration of activity of testosterone acetate when presented in the form of microbeads in accordance with the invention as compared with a conventional presentation was undertaken using the technique described by SAKAMOTO *et al., Proc. Soc. exp. biol. Med.*, (1951), *76*, 406.

Groups of male rats, each consisting of five rats aged about four weeks, were castrated. The rats in some groups were then treated by a single subcutaneous injection of 1 ml of an aqueous suspension of microbeads prepared as described in Example 4 (and containing 5 mg of testosterone acetate, together with 20 mg of polymer coating). Other groups of the rats were similarly injected with an aqueous suspension of 5 mg of testosterone acetate, still further groups were similarly injected with an oily solution of 5 mg of testosterone acetate, and of course yet other groups were left untreated to serve as controls.

The groups of five animals, both treated and untreated, were sacrificed at intervals after the day of treatment, as indicated in the Table of Results set out below, which also records the average increase (for that group) in the weight of the prostate gland, as a measure of the androgenic effect of the product tested.

The results obtained are listed in the following table:—

TABLE OF RESULTS

Treatment	Weight of the prostate in mg after: 4 days	8 days	15 days	22 days	29 days	36 days	43 days	50 days
Control	15.3	16.3	11.6	13.1	8.4	10.2	10.9	9.2
Aqueous Suspension		130.3		32.2				
Oily Solution		72.7		32.8				
Microbeads	90.5	182.4	167.9	113.7	78.1	69.9	74.3	53.6

From these results its is clear that testosterone acetate, when administered in the form of microbeads, still exerts a significant degree of stimulation upon the prostate 50 days after injection, whereas when administered as either an aqueous suspension or an oily solution, the degree of stimulation had become weak only 22 days after the injection. This clearly shows how significantly the presentation of the testosterone acetate in the form of microbeads can modify and extend its pattern of activity.

Example 10.
Tolerance Studies

The microbeads prepared in Example 4 were formulated into an aqueous suspension, and injected subcutaneously into rats. Observation was maintained on the rats for fifty days and for the entire length of the test the tolerance was found to be very good. Similar studies, in which the microbeads were injected intramuscularly into rabbits of the "Normande" breed, also showed the tolerance to be very good.

WHAT WE CLAIM IS:—

1. A process for preparing microbeads which comprise at least one water-insoluble or sparingly water-soluble pharmaceutically-active ingredient enclosed within a mantle composed of at least one methacrylic polymer (as hereinbefore defined), the mean diameter of the said microbeads being within the range of from 1 micron to 90 microns, in which an organic phase, comprising the methacrylic monomer or mixture of methacrylic monomers, a cross-linking agent for the monomer(s) and the water-insoluble or sparingly water-soluble pharmaceutically-active ingredient(s), is emulsified in an aqueous phase containing one or more salt(s) under agitation with a rotary stirrer running at a speed of at least 1,000 revolutions per minute, a polymerisation catalyst is then added to the emulsion thus formed, the polymerization is allowed to proceed, and the microbeads thus formed are recovered.

2. A process as claimed in claim 1, in which the aqueous phase employed contains an emulsifying agent and/or an anti-coalescing agent.

3. A process as claimed in claim 1 or claim 2, in which the organic phase employed contains an emulsifying agent, a plasticizing agent and a hardening agent.

4. A process as claimed in any of claims 1 to 3, in which the salt included in the aqueous phase is an alkali metal, alkaline earth metal or ammonium sulphate.

5. A process as claimed in claim 4, in which the sulphate used is sodium or ammonium sulphate.

6. A process as claimed in any of claims 1 to 5, in which the aqueous phase includes a sorbitan polyoxyethylene mono-oleic ester as emulsifying agent.

7. A process as claimed in any of claims 1 to 6, in which the aqueous phase includes a carboxyvinylic polymer as anti-coalescing agent.

8. A process as claimed in any of claims 1 to 7, in which the methacrylic monomer or mixture of methacrylic monomers used in the organic phase is or are methacrylic acid and/or an alkyl methacrylate.

9. A process as claimed in claim 8, in which the alkyl methacrylate is methyl methacrylate and/or butyl methacrylate.

10. A process as claimed in any of claims 1 to 9, in which the cross-linking agent for the monomer used in the organic phase is divinylbenzene.

11. A process as claimed in any of claims 1 to 10, in which the emulsifying agent used in the organic phase is a mixture of saturated high molecular weight fatty acid mono- and di-glycerides.

12. A process as claimed in any of claims 1 to 11, in which the plasticizing agent used in the organic phase is an alkyl sebacate.

13. A process as claimed in claim 12, in which the plasticizing agent is or includes diethyl or dioctyl sebacate.

14. A process as claimed in any of claims 1 to 13, in which the hardening agent used in the organic phase is polyvinyl acetate.

15. A process as claimed in any of claims 1 to 14, in which the catalyst used is 2,2' - azo *bis* - *iso*butyronitrile.

16. A process as claimed in any of claims 1 to 15, in which the emulsification of the organic phase in the aqueous phase is effected at a temperature within the range of from 60°C to 90°C.

17. A process as claimed in any of claims 1 to 16, and substantially as herein described.

18. Microbeads whenever prepared in or by the process claimed in any of claims 1 to 17.

19. Pharmaceutical compositions which comprise microbeads as claimed in claim 18, suspended or otherwise dispersed in a suitable aqueous or oily pharmaceutical vehicle (as herein defined) to form a sterile injectable liquid dispersion.

20. Pharmaceutical compositions as claimed in claim 19 and substantially as herein described.

21. Pharmaceutical compositions as claimed in claim 19 or claim 20 and substantially as herein described and illustrated in any of the Examples.

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